**Possible proinflammatory role of estrogen: implications on cGas-Sting-Tbk1 signaling in breast cancer.**

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Estrogens (E2) play a crucial role in the development and function of mammary tissue, promoting mammary gland cells growth. However, high E2 concentrations and longer lifetime exposure have been shown to increase breast cancer incidence, inducing cell cycle progression, and proliferation. Recently studies demonstrate that high estrogen-dependent transcriptional activity determine genomic instability through R-loops formation, which lead to DSB. Here, we searched for the influence of E2 on the inflammatory process and the consequent cGas-Sting-Tbk1 signaling activation. To evaluate the pro-inflammatory role of estrogen, MCF7 cells were treated or not with 1mM ICI ( ERα antagonist) and 10 µM cGAS i ( cGMP-AMP synthase inhibitor ) for 30’, in the presence or in the absence of E2. Through **γ**H2AX analysis, we showed that DNA damage increased in presence of E2; in the presence of ICI decreased; cGasi in co-treatment with E2 determined a rapid (2h) increased of **γ**H2AX levels that decreased after 24 h. These data suggested an involvement of cGAS in E2-induced oxidative DNA damage. Cell cycle analysis demonstrated that in the presence of cGasi, E2-induced cell cycle was impaired. Furthermore, Western blot analyses showed that the activation of Irf3, by Tbk1 is induced by E2 and mediated by cGas in vitro; treatment with selective inhibitors blocks or reduces its phosphorylation. E2 effects are influenced by many factors, such as immune stimulus, ERα and ERβ receptors expression and E2 intracellular metabolism. It has been shown that cGas-Sting-Tbk1 signaling can influence tumor microenvironment and immune response; preliminary data collected in this work, showed for the first time, the correlation between cGas-Sting-Tbk1 signaling and E2 role in inflammation. This work may have important implications in breast cancer treatment opening up new research perspectives in immunology and hormone therapy against cancer.